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Lumbar sympathectomy versus prostanoids for critical limb ischaemia due to non-reconstructable peripheral arterial disease

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What's new

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History

Date	Event	Description

Abstract

Background

Peripheral arterial disease (PAD) is a common circulatory problem that can lead to reduced blood flow to the limbs, which may result in critical limb ischaemia (CLI), a painful manifestation that occurs when a person is at rest. The mainstay of treatment for CLI is surgical or endovascular repair. However, when these means of treatment are not suitable, due to anatomical reasons or comorbidities, treatment for their pain is limited. Lumbar sympathectomy and prostanoids have both been shown to reduce pain from CLI in people who suffer from non-reconstructable PAD but there is currently insufficient evidence to determine if one treatment is superior. Due to the severity of the rest pain caused by CLI and its impact on quality of life it is important that people are receiving the best pain relief treatment available, therefore interest in this area of research is high.

Objectives

To compare the efficacy of lumbar sympathectomy versus prostanoid infusion in improving symptoms and function and avoiding amputation in people with CLI due to non-reconstructable PAD.

Search methods

The Cochrane Vascular Information Specialist searched the Specialised Register (last searched 29 March 2017) and

CENTRAL (2017, Issue 2). The Cochrane Vascular Information Specialist also searched clinical trials databases for ongoing or unpublished studies.

Selection criteria

Randomised controlled trials, with parallel treatment groups, that compared lumbar sympathectomy (surgical or chemical) versus prostanoids (any type and dosage) in people with CLI due to non-reconstructable PAD.

Data collection and analysis

Three review authors independently selected trials and extracted data. Any disagreements were resolved by discussion. We performed fixed-effect model meta-analyses, when there was no overt sign of heterogeneity, with risk ratios (RRs) and 95% confidence intervals (CIs).

Main results

A single study was included in this review comparing lumbar sympathectomy with prostanoids for the treatment of CLI in people with non-reconstructable PAD. The single study included 200 participants with Buerger's disease, a form of PAD, 100 in each treatment group, but only 162 were actually included in the analyses. The study compared an open surgical technique for lumbar sympathectomy with the prostanoid iloprost and followed participants for 24 weeks.

Methodological quality was good with low risk of bias for most evaluated domains. Due to the nature of the treatment, blinding of the participants and those providing the treatment would be impossible as a surgical procedure was compared with intravenous injections. It was not mentioned if blinded assessors evaluated the study outcomes. Therefore, we graded subjective outcomes (i.e. pain reduction) as unclear risk of detection bias and objective outcomes (i.e. ulcer healing, amputation and mortality) as low risk of detection bias. We also rated the risk of attrition bias as unclear; 38 out of 200 (19%) participants were not included in the analysis without clear explanation. A total 16 of 100 in the iloprost arm and 22 of 100 in the sympathectomy arm were not included in the analyses. The quality of evidence according to GRADE was low due to serious imprecision because the study numbers were low and there was only one study included.

The single included study reported on the outcome of complete healing without pain or major amputation, which fell under three separate outcomes for our review: relief of rest pain, complete ulcer healing and avoidance of major amputation. We chose to keep the outcome as a singularly reported outcome in order to not introduce bias in to the outcomes, which may have been the case if reported separately. The limited evidence suggests participants who received prostaglandins had improved complete ulcer healing without rest pain or major amputation when compared with those who received lumbar sympathectomy (RR 1.63, 95% CI 1.30 to 2.05) but as it was the only included study the data was rated as low quality and no overall conclusions can be drawn. The authors stated more participants who received prostaglandins reported adverse effects, such as headache, flushing, nausea and abdominal discomfort, but only one participant experienced severe enough adverse effects to drop out. Five participants who underwent lumbar sympathectomy reported minor wound infection (low-quality evidence). There was no reported mortality in either of the treatment groups (low-quality evidence).

The included study did not report on claudication distances and quality of life or functional status, or ankle brachial pressure index (ABPI), tissue oxygenation or toe pressures and progression to minor amputation, complications or provide any cost-effectiveness data.

Authors' conclusions

Low-quality evidence from a single study in a select group of people (people with Buerger's disease) suggests that prostaglandins are superior to surgical lumbar sympathectomy for complete ulcer healing without rest pain or major amputation, but possibly incur more adverse effects. Further studies are needed to better understand if prostaglandins truly are more efficacious than lumbar sympathectomy and if there are any concerns with adverse effects. It would be of great importance for future studies to include other forms of PAD, as Buerger's disease is a select type of PAD, data on quality of life, complications and cost-effectiveness data.

Plain language summary

Lumbar sympathectomy versus prostanoids for critical limb ischaemia due to non-reconstructable peripheral arterial disease

Background

People with peripheral arterial disease (PAD) have narrowed arteries which means it can be difficult to get sufficient blood to the extremities of the body, especially the legs. This lack of blood flow (ischaemia) over a long period can become painful. The pain usually becomes apparent only when a person has been walking a certain distance (intermittent claudication), but as the disease progresses the lack of blood flow worsens and the person may experience extreme pain while at rest (critical limb ischaemia (CLI)). Generally, if a person's blood vessels are in good enough health and the person does not suffer other illnesses that could complicate general anaesthesia, surgical repair of the arteries is considered and could help reduce ischaemic pain. However, in some people such a repair is not advised or possible, and their pain relief options are limited. Lumbar sympathectomy, which can be carried out by surgical or chemical approaches, and the use of intravenous prostaglandins, can help improve blood flow and reduce pain. Both have been shown to help reduce rest pain in people who cannot have surgical repair. It is unclear at this time which of these techniques is superior for pain reduction, ulcer healing, reduction in amputation or other outcomes important to people with CLI.

Study characteristics and key results

For this review we only identified one study that met the inclusion criteria (current until 29 March 2017). This study randomised 200 participants (162 included in analysis) and compared lumbar sympathectomy with the prostaglandin iloprost in people with Buerger's disease, a form of peripheral arterial disease, and followed participants for 24 weeks. This study found evidence of increased complete ulcer healing without rest pain or major amputation in the participants who received intravenous prostaglandin compared with those that received lumbar sympathectomy. However, those who received prostaglandins were more likely to report adverse events such as headache, flushing, nausea and abdominal discomfort. There were no reported deaths in either treatment group. The single included study did not report on other planned outcomes for this review such as walking distances and quality of life or functional status, and was limited to the specific form of PAD known as Buerger's disease, making it difficult to generalise the findings to all types of PAD.

Quality of evidence

Overall, the study was of good methodological quality and had little risk of bias due to design. Blinding of the participants and those that administered the treatment would be impossible, but there was no mention of blinding of the people who evaluated the outcomes, which would have been a possibility. Due to this, we rated the outcomes that had subjective measures (relief of rest pain) as unclear risk of bias, but the outcomes that had objective measures (ulcer healing, amputation and mortality) as low risk of bias. Also, there was a large number of participants not included in the analysis (38 of the 200, 19%), in both groups, and there was inadequate reasons given why, so we rated attrition bias as unclear. The quality of the evidence, as evaluated by GRADE, was low for the outcomes evaluated as the number of participants included was low and only a single study was reporting.

Background

Lower limb peripheral artery disease (PAD) refers to the obstruction or narrowing of the large arteries of the lower limbs, most commonly caused by atheromatous plaque or a thrombus (blood clot). The most common cause of PAD is atherosclerosis, which affects more than 200 million people worldwide (Kullo 2016). Risk factors for PAD include smoking, diabetes, hypertension and high cholesterol (Faglia 2009; Fowkes 2013). People who suffer from PAD have a greatly increased risk of suffering from cardiovascular problems including myocardial infarction, stroke and death from cardiovascular disease (Steg 2007).

It has been estimated that PAD is prevalent in about 3% - 10% of the population (Norgren 2007). Patients with PAD often present with muscle pain in the leg from mild exertion, such as walking (intermittent claudication (IC)), or decreased blood flow to the legs that can be painful at rest (critical limb ischaemia (CLI)). In a study from 2001 that included a population of participants with PAD, 32% of participants presented with pain during exertion, or IC (McDermott 2001). Intermittent claudication is often an early symptom of PAD and has a low long-term amputation rate. Critical limb ischaemia is characterised by severe pain at rest or tissue loss (ulceration or gangrene), or both. For people with PAD the 10-year risk of developing CLI is 30% (Aquino 2001).

Diagnosis of PAD is commonly achieved by measuring the ankle brachial index (ABI) which is a measure of the systolic blood pressure of the posterior tibial and dorsalis pedis arteries (arteries near ankle and the big toe, respectively), normalised to the brachial pressure (NICE 2012; Norgren 2007). A lower ABI indicates PAD, with the cut-off being 0.90 (Hirsh 2001). The Fontaine Classification system is commonly used to grade the severity of PAD. The Fontaine Classification systems ranges from stage I, which indicates the person is asymptomatic, up to stage IV, indicating the presence of ulceration and gangrene (Fontaine 1954).

NICE guidelines recommend treatment of IC with exercise in the first instance, after which treatment with pharmacotherapy, specifically the vasodilator naftidrofuryl oxalate, is recommended if exercise alone does not alleviate symptoms (NICE 2012). Endovascular procedures such as angioplasty and stenting, as well as bypass surgery are only considered if other forms of treatment do not relieve symptoms of IC (NICE 2012; Norgren 2007). Angioplasty or bypass are recommended treatment strategies for patients with CLI, as well as pain management with paracetamol or opioids (NICE 2012; Norgren 2007). Amputation is only considered for PAD if all other treatment options are exhausted or found to not be suitable.

Treatment of PAD with amputation of the affected limb has been decreasing, which has coincided with an increase in surgical and endovascular procedures to improve blood flow (Rowe 2009). However, many patients have non-reconstructable disease with very poor distal blood flow and often undergo major amputation for the relief of rest pain. Amputation rates for pain relief in these patients are high, up to 45%, because the treatment options are very limited (Dormandy 1999). Lumbar sympathectomy and prostanoid infusion are alternative treatment options for people with PAD who are not suitable for endovascular or surgical treatment (Diehm 2004; Lee 2006; Pieri 2005).

Description of the intervention

Lumbar sympathectomy and prostanoids have both been shown to result in relief of rest pain and promote ulcer healing in patients with CLI due to PAD.

Lumbar sympathectomy is a procedure that disrupts the sympathetic chain in the lumbar region of the spinal cord which is generally performed to increase blood flow and/or reduce pain. This procedure can be performed using a radiologically guided chemical injection or by a surgical procedure. Radiographically guided chemical lumbar sympathectomy is carried out by injection of a chemical agent in to the lumbar sympathetic ganglia under computer tomography (CT) guidance, usually at the L3 level to achieve neurolysis of the lumbar sympathetic chain. Surgery involves surgical division of the sympathetic chain, which can be done via open surgery or laparoscopically. In the past, blind sympathectomy was also done but this has now been largely abandoned due to the availability of CT (Tay 2002).

Prostanoids are a group of lipid compounds that, when given intravenously, act as a vasodilator and reduce blood platelet aggregation. The evidence is mixed regarding prostanoids as a method for pain relief for PAD, as well as the ability of the treatment to improve ulcer healing, increase limb salvage and improve mortality, with some studies saying they do improve symptoms and others saying there is no effect (Abu Dabrh 2015; Robertson 2013; Ruffolo 2010).

How the intervention might work

Lumbar sympathectomy works by disruption of the efferent autonomic pain pathways and reduction of vasoconstriction caused by sympathetic nerves. The resulting vasoconstriction leads to distal reperfusion and pain relief (Tay 2002).

Prostanoids are thought to act by causing an alteration in tissue perfusion by changing small artery compliance and helping to increase blood flow to ischaemic limbs as well as helping to protect the endothelium. Prostanoids act as a vasodilatory and antithrombotic agent. Common prostanoids include prostaglandin E1 (PGE1) and the prostacyclin derivative iloprost (Norgren 2007).

Why it is important to do this review

Patients with symptomatic PAD often present with claudication and rest pain. While some patients can achieve pain relief through angioplasty or bypass procedures, many are not suitable for such procedures and pain needs to be managed in alternative way. Pain relief and ulcer healing in this group of patients are traditionally managed by sympathectomy but the amputation rates for pain relief in these patients are high (up to 45%). Recent trials on prostanoid use have shown positive outcomes for pain relief and ulcer healing in this patient group but results are inconsistent. A systematic review of well-conducted and reported randomised controlled trials is required to evaluate the comparative efficacy of sympathectomy versus prostanoid use. If pain relief, limb salvage and functional outcomes with prostanoid use are comparable to sympathectomy, patients may be able to avoid a radiological procedure or surgery (sympathectomy).

Objectives

To compare the efficacy of lumbar sympathectomy versus prostanoid infusion in improving symptoms and function and avoiding amputation in people with CLI due to non-reconstructable PAD.

Methods

Criteria for considering studies for this review

Types of studies

We included one parallel-group randomised controlled trial (RCT) of lumbar sympathectomy versus prostanoids.

Types of participants

We included participants with CLI due to non-reconstructable PAD.

We define CLI as rest pain for more than two weeks requiring analgesics, or tissue loss (ulceration or gangrene), or the participant meets at least one of the following diagnostic criteria in the affected limb:

1. ankle artery occlusion absolute pressure < 50 mmHg or ankle brachial pressure index (ABPI) < 0.4

2. toe pressure < 40 mmHg

3. transcutaneous oxygen measurement ($TcPO_2$) < 20 mmHg when lying down breathing room air, if available

We define non-reconstructable as the following: there is no reasonable open surgical or endovascular revascularisation option as determined by the treating vascular specialist. Factors that may contribute to the determination of inoperability include the following:

1. Anatomical considerations:

- no outflow targets
- no appropriate conduit (i.e. vein for bypass)
- long segment occlusions or calcified lesions that predict poor outcome with endovascular approaches

2. High risk medical conditions:

- unstable cardiac disease
- renal insufficiency
- uncontrolled diabetes

3. History of prior failed revascularisation attempts

4. Primary assessment of vascular operability was performed by the vascular surgeon. If anatomical considerations were invoked, a second physician may be consulted. The second physician could be a vascular surgeon, interventional radiologist, cardiologist, or vascular medicine specialist.

Types of interventions

We included one study that compared treatment with lumbar sympathectomy versus prostanoids for PAD. Lumbar sympathectomy could be undertaken chemically or surgically (open or blind), as well as unilateral or bilateral. We included any dosage and type of prostanoids, including, but not limited to, prostaglandin E1 (PGE1) and prostacyclin (PGI).

Types of outcome measures

Primary outcomes

1. Relief of rest pain
2. Ulcer healing
3. Avoidance of major amputation

Secondary outcomes

1. Intermittent and absolute claudication distance (pain-free walking distance and maximum walking distance, respectively)
2. ABPI, tissue oxygenation ($TcPO_2$) and toe pressure
3. Progression to minor amputation
4. Quality of life and functional status
5. Adverse effects
6. Complications
7. Mortality
8. Analysis of cost effectiveness (if data are available)

Outcomes are classified as short term (within six months), medium term (over six months to two years), and long term (more than two years)

Search methods for identification of studies

We applied no language restriction on publications.

Electronic searches

The Cochrane Vascular Information Specialist (CIS) searched the following databases for relevant trials:

- The Cochrane Vascular Specialised Register (29 March 2017);
- The Cochrane Central Register of Controlled Trials (CENTRAL (2017, Issue 2)) via The Cochrane Register of Studies Online.

See Appendix 1 for details of the search strategy used to search CENTRAL.

The Cochrane Vascular Specialised Register is maintained by the CIS and is constructed from weekly electronic searches of MEDLINE Ovid, Embase Ovid, CINAHL, AMED, and through handsearching relevant journals. The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Vascular module in the Cochrane Library (www.cochranelibrary.com).

The CIS also searched the following trials registries for details of ongoing and unpublished studies (29 March 2017);

- CinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch);
- ISRCTN Register (www.isrctn.com/).

See Appendix 2 for details of these searches.

Searching other resources

We scrutinised bibliographies of relevant publications found from the electronic searches to identify any further randomised trials. We contacted authors of trials for further information in cases where there were missing data or doubts about whether to include the trials in the review. We contacted authors of identified potentially relevant published RCTs in order to get further information about published or unpublished studies.

Data collection and analysis

The software used for preparing and maintaining Cochrane Reviews (RevMan 5.3), was used to compile data and generate meta-analysis.

Selection of studies

Three review authors (IS, SA and PT) independently selected trials for inclusion. In the event of disagreements, we reached consensus by referral to the original report, contacting authors of trials, and through discussion.

Data extraction and management

Three review authors (IS, SA and PT) independently extracted data using a standardised form. We extracted data that included information regarding the trial design, patient characteristics (for example diabetes, hypertension, systemic disease, past interventions, drug history, functional status and other demographic data), therapy type, dosages, treatment periods/duration, and for sympathectomy, the spinal level it was performed at. We collected information on relief of rest pain, ulcer healing, pain-free walking, maximum walking distances and any other available outcomes. We also collected information on adverse effects from each trial. Where necessary, we sought information from the principal authors of the included studies. The three review authors that performed data extraction cross-checked the extracted data for verification.

Assessment of risk of bias in included studies

Risk of bias in the one included trial was evaluated independently by three review authors (IS, SA and PT) on the following six components: selection bias (sequence generation and allocation concealment), performance and

detection bias (blinding), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other biases. For each of these components, we assigned a judgement regarding the risk of bias as high, low or unclear (Higgins 2011). Blinding of participants and investigators would not be achievable due to the nature of the treatments so performance bias is not specifically assessed. For detection bias we made judgements separately for objectively and subjectively ascertained measures. We recorded these assessments for the included study in the standard 'Risk of bias' tables. We used these assessments in making judgements on overall study quality while preparing a 'Summary of findings' table. We attempted to contact the trial authors for clarification when methodological details were unclear. We resolved differences by discussion.

Measures of treatment effect

We utilised a fixed-effect model to generate risk ratios (RR) and 95% confidence intervals (CI) of homogeneous dichotomous data for each outcome with sufficient data. We planned to combined continuous variables in to the mean difference with 95% CIs.

Unit of analysis issues

We only included one simple parallel-group design study. The individual participant is the unit of analysis.

Dealing with missing data

We attempted to obtain missing data from trial authors. Where possible, we extracted data to allow an intention-to-treat (ITT) analysis in which all randomised participants are analysed in the groups to which they were originally randomised. If there was a discrepancy in the numbers randomised and the numbers analysed in each treatment group, we calculated the percentage lost-to-follow up in each group and reported this information. If dropouts exceed 10%, we assigned the worse outcome to those lost to follow-up for dichotomous outcomes and assessed the impact of this in sensitivity analyses with the results of completers.

For continuous data that were missing standard deviations, we planned to either calculate these from other available data such as standard errors, or impute them using methods suggested in Deeks 2008. We did not intend to make any assumptions about loss-to-follow up for continuous data and planned to analyse results for those who completed the trial.

Assessment of heterogeneity

We planned to assess heterogeneity between the trials by visual examination of the forest plot to check for consistency in the direction of effect estimates and for overlapping confidence intervals. We planned to use the Chi^2 test for homogeneity at a 10% level of significance to detect statistical heterogeneity. We planned to use the I^2 statistic to assess inconsistency (the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error) (Higgins 2002). We intended to interpret a value of I^2 of 50% or greater to denote significant heterogeneity and utilise a random-effects model.If severe heterogeneity was present (I^2 >= 75%) and could not be explained by differences across the trials in terms of clinical or methodological features or by subgroup analyses (see below), we intended to not combine the trials in a meta-analysis but present the results in a forest plot.

Assessment of reporting biases

We assessed the included study for adequacy of reporting of data for pre-stated outcomes and for selective reporting of outcomes. We noted judgements based on the risk of selective reporting in the 'Risk of bias' table in the Characteristics of included studies table. We reported risk of selective outcome reporting in the results under Risk of bias in included studies. We planned to assess the likelihood of potential publication bias using funnel plots (Egger 1997), provided that there were at least 10 trials assessing particular outcomes in a meta-analysis.

Data synthesis

We synthesised dichotomous data with the Mantel-Haenszel method to derive pooled, weighted risk ratios. We planned to combine continuous data summarised by arithmetic means and standard deviations using the inverse variance method to derive the weighted mean difference. If the same continuous outcomes in studies were measured using different scales, we planned to use the inverse variance method to derive standardised mean difference and express the pooled results as odds ratios and as absolute measures using methods described in Deeks 2008.

Subgroup analysis and investigation of heterogeneity

If data permitted, we planned to carry out subgroup analyses using the following subgroups: age, sex, diabetes, cardiac comorbidity, and disease type (thromboangitis obliterans (TAO or Buergers disease), atherosclerosis, vasculitis), as well duration of follow-up (short, medium, and long term).

Sensitivity analysis

We intended to undertake sensitivity analyses if trials reported dropout rates of 10% or greater, to ascertain differences in outcomes of ITT analysis (all dropouts were assigned to the worst outcome for dichotomous outcomes) and analysis of completers as described in Dealing with missing data. However, due to the high number of dropouts in the single included study we chose to report a per protocol analysis (only reporting those who actually had follow-up information) as our main analyses and then use an ITT analyses for the sensitivity analysis, with the dropouts assigned the worst outcome. We felt this best demonstrated the actual data collected without making assumptions about the large number of dropouts.

We planned to calculate the results using all studies and then evaluate the exclusion of studies judged to be at high risk of bias for the primary outcomes across the domains evaluated. We also planned to assess the estimates of effect with and

without missing data imputation, if such data were included.

Summarising and interpreting results

We used the GRADE approach to interpreting findings (Schünemann 2011), and used the online GRADEpro GDT software (GRADEpro GDT 2015) to create a 'Summary of findings' table with information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the following seven critically important outcomes: relief of rest pain, complete ulcer healing, avoidance of amputation, intermittent and absolute claudication distances, quality of life and functional status, adverse effects, and mortality, from each included study in the comparison.

Results

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies

Results of the search

We retrieved three reports from the performed searches. We obtained the full text for these reports to assess their eligibility. After we excluded irrelevant reports, we identified only a single study (two reports) for inclusion. The full study selection flow diagram can be found in Figure 1.

Included studies

Bozkurt 2006 was the only study that met the inclusion criteria and is described more thoroughly in the Characteristics of included studies table. This study was a randomised parallel group, multi-centre controlled clinical trial. A total of 200 participants diagnosed with a form arterial disease, called Buerger's disease, were randomised in the study, 162 were analysed. This study compared the prostaglandin iloprost with lumbar sympathectomy by open surgery. Outcome measures analysed were complete ulcer healing, relief of ischaemic rest pain, avoidance of major amputation, complications, adverse effects and mortality. The trial assessed outcomes at 4 weeks and 24 weeks; for our analysis we used data at 24 weeks.

Excluded studies

The Petronella 2004 study was excluded from our review. Further information can be found in the Characteristics of excluded studies table. This study did not match our inclusion criteria as it included some patients requiring surgical revascularisation. This is likely to influence the outcome of the intervention under study. Surgical revascularisation is the first line of management for CLI, without which relief of ischaemic pain is low and rates of limb loss are high. Treating such a patient group with prostaglandin or sympathectomy may cause a delay in revascularisation and theoretically worsen the stage of ischaemia. Performance of revascularisation after the trial intervention also influences the outcome follow-up: patients with successful revascularisation will report better outcomes. It would then be unclear if this improvement is because of the study intervention or the revascularisation. The authors state that "the patients were randomly allocated...though they were well matched in terms of disease status". There was no sample size calculation and the method of randomisation, allocation concealment etc was unclear. The study also included a few patients with early stages of disease, again, prostaglandin or sympathectomy are not acceptable treatment modalities in such patients.

Risk of bias in included studies

The assessments regarding the risk of bias for are depicted in Figure 2 and Figure 3.

Allocation (selection bias)

A computer-generated random sequence that was produced by an independent statistician was utilised for randomisation so Bozkurt 2006 was judged to be free of the risk of selection bias for sequence generation and allocation concealment.

Blinding (performance bias and detection bias)

Due to the nature of the interventions, injection of prostaglandin versus open surgical lumbar sympathectomy, blinding of the participants and investigators (performance bias) could not be sufficiently carried out. The risk of detection bias in the included trial was assessed separately with regard to the subjective and objective outcomes.

Subjective outcomes (pain) was considered to have an unclear risk of bias. The study authors report the change in the clinical severity as indirect evidence of improvement in pain but there was no objective pain measure score reported in the trial. It was not indicated by the study authors if a blind assessor was utilised to collect outcome data.

Objective outcomes (amputation, ulcer healing) were judged to have a low risk of bias. Ulcer healing was assessed by objective measurement of ulcer size and backed-up with follow-up data. Amputation is a definitive clinical endpoint so the risk of detection bias for the objective outcomes was low.

Incomplete outcome data (attrition bias)

Of the 200 patients randomised, only 162 were included in the analysis and the authors stated that there were "insufficient data for the remaining patients". In both groups there were participants not included (n = 16 in the iloprost arm, n = 22 in the sympathectomy arm), but no reasons were given for why the participant data were not available. We judged the attrition bias to be unclear and because this was the only included study we reported the outcomes as a per-protocol analysis and a separate ITT analysis with all dropouts assumed to have the worst outcome.

Selective reporting (reporting bias)

Although the trial was not registered, all proposed outcome measures were reported. We judged the risk of reporting bias to be low.

Other potential sources of bias

We could not identify any other potential source of bias in this trial.

Effects of interventions

All outcomes reported are from a single trial (Bozkurt 2006). The trial did not report data on intermittent or absolute claudication distance, ABPI, tissue oxygenation ($TcPO_2$), toe pressure, progression to minor amputation, quality of life/ functional status or analysis of cost effectiveness. Bozkurt 2006's main outcome was "complete healing without pain or major amputation" which we believe fits the criteria for our outcomes of 'complete ulcer healing', 'avoidance of amputation' and 'pain relief'. As this was the only included study we chose to report the findings as they were presented in the study, as a single outcome, in order to reduce the risk of bias when presenting the results.

Also, we intended to report the outcomes in an ITT analysis, but due to the large number of dropouts we decided to present the primary analysis on a per-protocol basis. We also included a secondary ITT analysis with dropouts assumed to have the worst outcome. We believe this addresses the discrepancy in participant numbers in a clear manner.

Complete ulcer healing without rest pain or major amputation.

For the single reporting study, there were 72 patients in the prostaglandin arm and the 41 in the sympathectomy arm who reported pain relief 24 weeks after treatment. These findings provide low-quality evidence in favour of prostaglandin as an intervention when compared with lumbar sympathectomy (RR 1.63, 95% CI 1.30 to 2.05; Analysis 1.1). The evidence for this outcome comes from only a single study so the quality has been graded as low due to serious imprecision.

Adverse effects

Insufficient data were provided in the single reporting study to include adverse effects in a meta-analysis. However, the authors of the study noted that more participants receiving the prostaglandin reported side effects which included headache, flushing, nausea and abdominal discomfort, but only one person in this group had to drop out due to symptoms. Five participants undergoing lumbar sympathectomy had minor wound infection.

Mortality

Bozkurt 2006 reported no mortality in either group so an overall risk ratio could not be calculated at this time (Analysis 1.3). The evidence was graded as low due to serious imprecision.

Sensitivity analysis

In the single included trial there is a large number of missing participant data in both arms with a total rate of 19%. Our primary analysis was based on a per protocol analysis, only those that received treatment and had follow-up data reported. For sensitivity analysis we have performed an ITT analysis, which includes all participants randomised and outcomes for those that were lost to follow-up to be imputed as the worst possible. For the outcome 'Complete ulcer healing without rest pain or major amputation' that means no further participants were added as events and for 'morality', all missing participants were assumed to have died.

For sensitivity analysis for 'Complete ulcer healing without rest pain or major amputation' when all participants randomised were included the strength of the point estimate and 95% CI increased, but the overall finds were unchanged (RR 1.76, 95% CI 1.35 to 2.29; Analysis 1.2).

Sensitivity analysis of mortality showed no evidence of a difference between the treatments (RR 0.73, 95% CI 0.41 to 1.30; Analysis 1.4).

Subgroup analysis

We could not perform subgroup analyses as results were only from a single trial that did not include subgroup level data.

Discussion

Summary of main results

The results of a single trial favour the use of prostaglandins for complete ulcer healing without rest pain or major amputation in patients presenting with critical limb ischaemia (CLI) and diagnosed to have non-reconstructable peripheral arterial disease (PAD) compared with surgical lumbar sympathectomy. This evidence was judged to be low-quality evidence. The study reported a possible increase in mild adverse events in the group that was assigned prostaglandins, and there were no reported deaths for either treatment group, both also judged as low-quality evidence. No data were provided on claudication distances, ABPI, tissue oxygenation ($TcPO_2$) and toe pressures, progression to minor amputation, quality of life and functional status, complications, analysis of cost effectiveness, or long-term outcomes.

Overall completeness and applicability of evidence

This review provides low-quality evidence on the benefit of use of prostaglandins in the management of patients presenting with non-reconstructable CLI. Only one study presented data sufficient to adequately address the objectives of this review. There were a high number of participants lost-to-follow-up without explanation, reducing the completeness of the reporting. The study only included patients with Buerger's disease, so this review provides evidence supporting the role of

prostaglandins in treatment of this patient group only. These results are significant as, unlike atherosclerotic disease which has better revascularisation options, Buerger's disease presents with higher rates of non-reconstructable disease. This leads to higher rates of limb loss and interventions so this demographic has a high clinical utility. However, those with Buerger's disease tend to have fewer systemic comorbidities than patients with atherosclerotic disease, making the findings of this review difficult to apply to other causes of PAD.

Management of patients with CLI is advancing rapidly with a fewer number of patients being treated as non-reconstructable. However, this advance in treatment options is not matched by an equivalent reduction in mortality or improvement in quality of life. These areas, as well as cost effectiveness of the interventions, are not considered in the included trial. This trial was performed in patients with Buerger's disease diagnosed by Shionoyas criteria, which excludes patients with atherosclerotic or other aetiologies in whom the interventions of interest would play a significant role, limiting the applicability of the evidence. Another issue reducing applicability of the evidence from the single study, is the fact that the included trial did not use other methods of sympathectomy (e.g. CT guided chemical sympathectomy or laparoscopic means), which arguably may yield better outcomes as they are less invasive and cause less disruption of the collateral vascular network. Also, there are inherent concerns with the assessment of ulcer healing. The included study did specify inclusion of those with ischaemic ulcers but they did not report their procedures for how they determined this. There is a risk the study included a mix of ulcers types (i.e. venous ulcers, neuropathic ulcers and ischaemic ulcers). Also, the methods of measuring ulcers can be quite variable, possibly biasing the results.

Treatment of PAD is rapidly changing and the definition of 'non-reconstructable PAD' shifts as new treatment becomes available and techniques are refined. As the single included study was reported over a decade ago, it is likely these participants would no longer fit the current definition of non-reconstructable PAD and also these treatment methods are not as commonly practiced. It should be noted that NICE guidelines currently only recommend lumbar sympathectomy in the context of a clinical trial as the outcomes for patients is unclear (NICE 2012).

Quality of the evidence

There is only a single trial included in this review, which limits the quality of evidence. Parallel searches confirmed that no published trials were missed out. The included trial was limited by its small size, lack of sample size calculation and participants missing from analysis due to insufficient data, thus the GRADE rating was low. A total of 200 participants were randomised, 100 in each study arm, but only 162 (81%) were included in the analysis, and there was insufficient information provided on why the 38 participants were not included. Sixteen of the 100 randomised to the iloprost arm were not included and 22 of the 100 in the sympathectomy arm were not included. However, the estimates calculated from the trial are reasonable and the confidence intervals are not overly large. Larger studies with longer duration of follow-up, including other patient subgroups are necessary.

Potential biases in the review process

All attempts to limit potential bias in the review were achieved by having multiple authors select studies to be included, execute data extraction and rate the quality of the study. We could not identify any potential biases in the review process. However, it should be noted that the single study included in the review reported a single outcome of "complete healing without pain or major amputation" which we believe fits the criteria for three separate outcomes in our review: 'complete ulcer healing', 'avoidance of amputation' and 'pain relief'. After careful consideration we decided to report the findings as a single outcome, to accurately reflect the data presented in the original study publication. This required us to deviate from the protocol, but this was deemed superior to potentially misrepresenting the findings.

Agreements and disagreements with other studies or reviews

We were unable to identify any other systematic review or meta-analysis comparing the use of lumbar sympathectomy and prostanoids in non-reconstructable CLI.

Revascularisation remains the first line of intervention in patients with CLI. Both lumbar sympathectomy and prostanoids have been identified to have positive results regarding rest-pain relief, ulcer healing and amputations in people for whom revascularisation is not an appropriate treatment. As there is no conclusive evidence of the long-term effectiveness and safety these treatment options are feasible only in patients with non-reconstructable arterial disease who are at high risk of limb loss (Ruffolo 2010).

Authors' conclusions

Implications for practice

Data from a single trial provide low-quality evidence to suggest that prostaglandins are superior to lumbar sympathectomy in producing complete ulcer healing without rest pain or major amputation. This evidence was derived from a single study conducted using a select group of people (with Buerger's disease). Prostaglandins appear to be well tolerated as compared to open lumbar sympathectomy although there were reports of mild adverse events. Costs and quality of life measures were not studied, therefore no clear indication can be given on these areas. However, these conclusions need verification in larger clinical trials including patients with other methods of sympathectomy and other aetiologies of PAD.

Implications for research

Further randomised trials are needed to more precisely define the relative and absolute benefits and risks of lumbar sympathectomy and prostaglandin infusion as treatment options in patients with non-reconstructable peripheral arterial disease presenting with CLI. Studies analysing the costs, quality of life outcomes and long-term outcomes of these treatment modalities are required.

Acknowledgements

The protocol for this review is an output of a protocol development workshop conducted by the Prof. BV Moses and ICMR Centre for Advanced Research and Training in Evidence-Informed Healthcare (Sen 2011).

Contributions of authors

IS: wrote protocol; trial selection, assessed quality, extracted data, performed meta-analyses, interpreted results, and wrote review manuscript
SA: helped writing the protocol; extracted data, interpreted results, and wrote review manuscript
PT: helped writing the protocol; assessed quality, extracted data, performed meta-analysis, and wrote review manuscript
RF: assisted in writing of the review manuscript and performing the meta-analysis

Declarations of interest

IS: none known
SA: none known
PT: PT's institution has received funding from the Indian Council for Medical Research (ICMR): the Professor BV Moses Centre was funded by an educational grant from the Indian Council for Medical Research during the development of the protocol for this systematic review
RF: none known

Differences between protocol and review

The outcome referring to walking distances has been modified to 'Intermittent and absolute claudication distance (pain-free walking distance and maximum walking distance, respectively)'. The two separate walking distances were clarified and 'increase in' was removed as we want to report any change in walking distances and not only if there is an increase.

The outcome of ABPI was edited to only 'ABPI' and 'improvement of' was removed as we intend to report on any ABPI findings and not only those that show improvement.

The protocol stated that an ITT analysis would be performed as the primary analysis where possible. After inclusion of only a single study with a high rate of unexplained dropouts, we chose to report a per protocol analysis as the primary analysis and include the ITT population in a sensitivity analysis.

We combined three individual primary outcomes of relief of rest pain, ulcer healing and avoidance of major amputation in to a single outcome to reflect the outcome reported in the only included study : Complete healing of ulcer without rest pain or major amputation. We chose to do this after careful consideration in order to reduce a possible bias when interpreting the individual outcomes.

Published notes

Characteristics of studies

Characteristics of included studies

Bozkurt 2006

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Methods	Design: randomised parallel group multi-centre controlled clinical trial Setting : 12 major vascular centres Country: Turkey Loss to follow-up: complete data from 162 patients presented in the analysis after a follow up of 4 and 24 weeks (19% of participants missing from analysis; 16% in iloprost group and 22% in sympathectomy group) Intention-to-treat: not stated
Participants	Number randomised n = 200 (iloprost n = 100; sympathectomy n = 100); number analysed at 24 weeks (iloprost n = 84; sympathectomy n = 78) Average age (range): 40.8 years (25 - 66) Gender: male: 97.6% No systemic comorbidities Inclusion criteria: 1. Buerger's disease diagnosed by Shionoyas criteria 2. Critical ischaemia - rest pain/ ischaemic ulcer Exclusion criteria: not mentioned
Interventions	Prostanoid iloprost; intravenous infusion 1ng/kg/min, six hours/day for 28 days Open surgical unilateral sympathectomy at lumbar levels 2, 3, 4
Outcomes	**Reported in paper, used in review** • relief of rest pain • ulcer healing • avoidance of major amputation • mortality • adverse events **Reported, not used** • change in ulcer size • 50% reduction in ulcer size • analgesic requirements • clinical improvement by SVS/ISCVS **Sought from authors: not reported** • claudication distances • ABPI, tissue oxygenation ($TcPO_2$), toe pressure • Progression to minor amputation • Quality of life and functional status • Analysis of cost effectiveness Duration of follow up: 24 weeks
Notes	Funding: Research fund of Istanbul University Comments : No conflicts of interest Trial was not registered

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote from report: "independent statistician prepared the randomisation list by the method of computer generated random numbers."
Allocation concealment (selection bias)	Low risk	Use of randomly generated list prepared by an independent statistician
Blinding (performance bias and detection bias) Subjective outcome (pain)	Unclear risk	Blinding of participants was not possible due to the nature of intervention - a drug was being compared to a surgical procedure. Pain is a subjective outcome and no data on objective recordings e.g. using pain scores is reported; it was not reported if a blinded assessor or adjudication committee was used
Blinding (performance bias and detection bias) Objective outcomes (amputation, healing)	Low risk	Amputation and ulcer healing are definite clinical outcomes, evidence of risk of bias for these outcomes is minimal. Data on objective documentation of ulcer healing are presented, which also reduces the risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	162 of 200 randomised participants included in analysis; both groups had similar numbers of dropouts: iloprost n = 16, sympathectomy n = 22; study quoted missing participant data as "insufficient data for the remaining participants" with no further information on reasons so we judged attrition bias as unclear
Selective reporting (reporting bias)	Low risk	Although the trial was not registered, all proposed outcome measures were reported adequately
Other bias	Low risk	None detected by the review authors

Footnotes

ABPI: ankle brachial pressure index
SVS/ISCVS: Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery

Characteristics of excluded studies

Petronella 2004

Reason for exclusion	The study did not match our inclusion criteria as it included some patients requiring surgical revascularisation. This is likely to influence the outcome of the intervention under study. Surgical revascularisation is the first line of management for critical ischaemia, without which relief of ischaemic pain is low and rates of limb loss are high. Treating such a patient group with prostaglandin or sympathectomy may cause a delay in revascularisation and theoretically worsen the stage of ischaemia. Performance of revascularisation after the trial intervention also influences the outcome follow up: patients with successful revascularisation will report better outcomes, which would then make it unclear if this improvement is because of the study intervention or the revascularisation. The study also included a few patients with early stages of disease, again prostaglandin or sympathectomy are not acceptable treatment modalities in such patients. Also, the method of randomisation and patient assignment was unclear.

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 Prostanoids versus lumbar sympathectomy for critical limb ischaemia due to non-reconstructable peripheral arterial disease

Prostanoids versus lumbar sympathectomy for critical limb ischaemia due to non-reconstructable peripheral arterial disease						
Patient or population: patients with critical limb ischaemia due to non-reconstructable peripheral arterial disease **Settings:** 12 centres in Turkey **Intervention:** prostanoids versus lumbar sympathectomy						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Lumbar sympathectomy	**Prostanoids**				
Complete ulcer healing without rest pain or major amputation (per-protocol) Clinical assessment Follow-up: 24 weeks	**526 per 1000**	**331 per 1000** (158 to 552)	**RR 1.63** (1.30 to 2.05))	162 (1 study)	⊕⊕⊖⊖ low[1]	The outcomes 'relief of rest pain', 'complete ulcer healing' and 'avoidance of amputation' were all derived from a single outcome reported by Bozkurt 2006 as "complete healing without pain or major amputation". We chose to deviate from the review protocol and combine the outcomes, reflecting the single included study in order to limit potential bias.
Intermittent and absolute claudication distances	See comment	See comment	Not estimable			Not reported on in included study
Quality of life and functional status	See comment	See comment	Not estimable			Not reported on in included study
Adverse effects Clinical assessment Follow-up: 24 weeks	See comment	See comment	Not estimable	162 (1 study)	⊕⊕⊖⊖ low[1]	Adverse effects were not reported in a way that we could include in an analysis. Authors of the one included study reported more adverse effects in participants that received prostaglandin, but only one participant withdrew due to adverse effects.
Mortality Clinical assessment Follow-up: 24 weeks	See comment	See comment	Not estimable	162 (1 study)	⊕⊕⊖⊖ low[1]	No mortality reported in this trial
*The basis for the **assumed risk** (e.g. the median control group risk across studies) is that the risk in the control group. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio.						
GRADE Working Group grades of evidence **High quality:** Further research is very unlikely to change our confidence in the estimate of effect. **Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low quality:** We are very uncertain about the estimate.						

Footnotes

[1] Downgraded by two levels due to serious imprecision: study sample size was small with significant dropouts, and the data were only from a single trial.

Additional tables

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* Bozkurt AK, Koksal C, Demirbas MY, Erdogan A, Rahman A, Demirkilic U, et al. A randomized trial of intravenous iloprost (a stable prostacyclin analogue) versus lumbar sympathectomy in the management of Buerger's disease. International Angiology 2006;25(2):162-8. [PubMed: 16763533]

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Studies awaiting classification

Ongoing studies

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Classification pending references

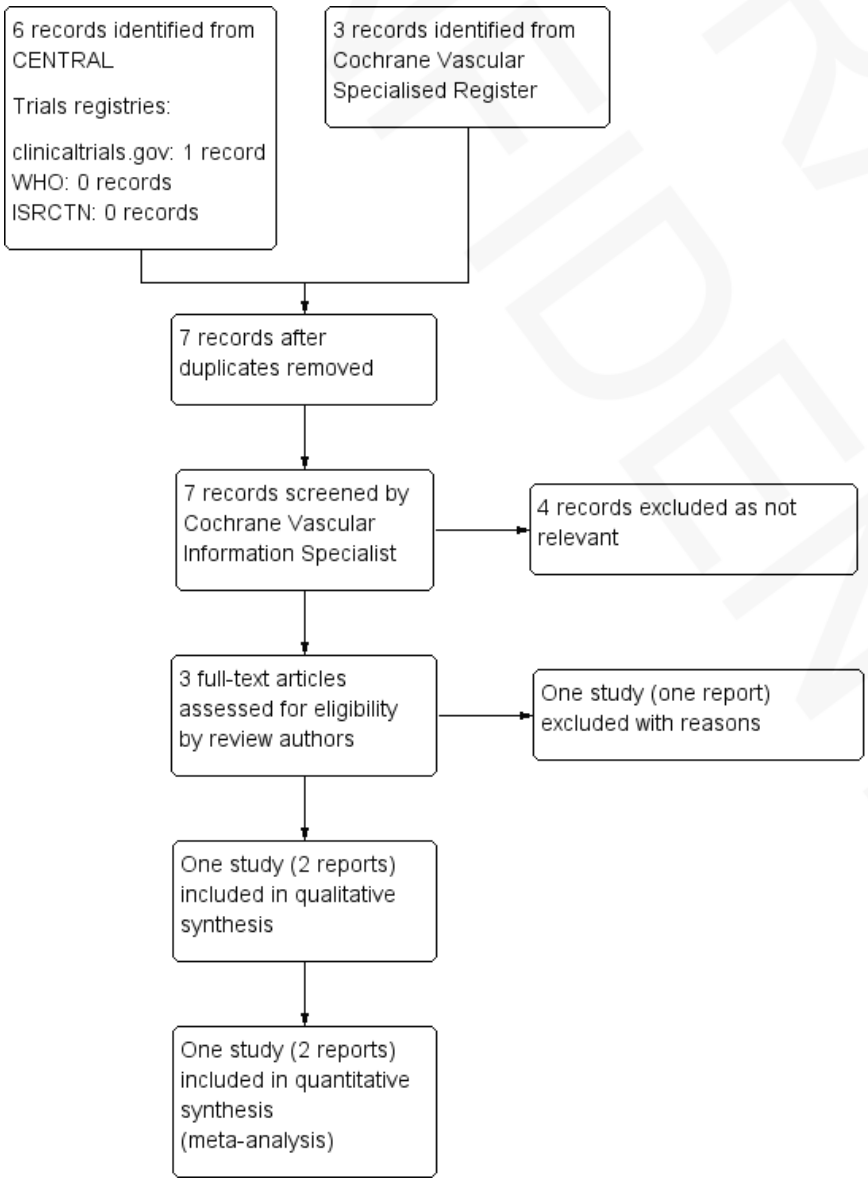
Data and analyses

1 Prostanoids versus lumbar sympathectomy

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Complete ulcer healing without rest pain or major amputation at 24 weeks (per-protocol analysis)	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.2 Complete ulcer healing without rest pain or major amputation at 24 weeks (ITT/sensitivity analysis)	1		Risk Ratio(M-H, Fixed, 95% CI)	Subtotals only
1.3 Mortality (per-protocol analysis)	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals
1.4 Mortality (ITT/sensitivity analysis)	1		Risk Ratio(M-H, Fixed, 95% CI)	No totals

Figures

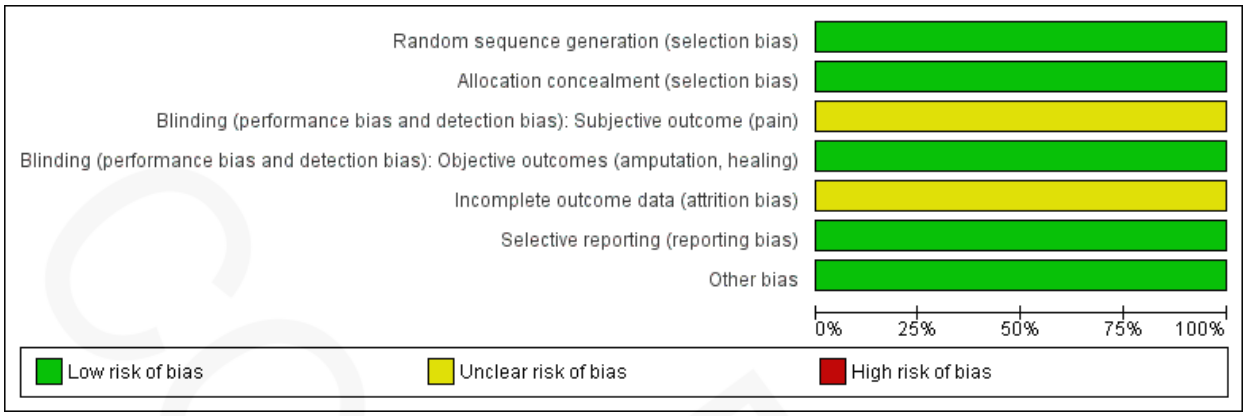
Figure 1



Caption

Study flow diagram.

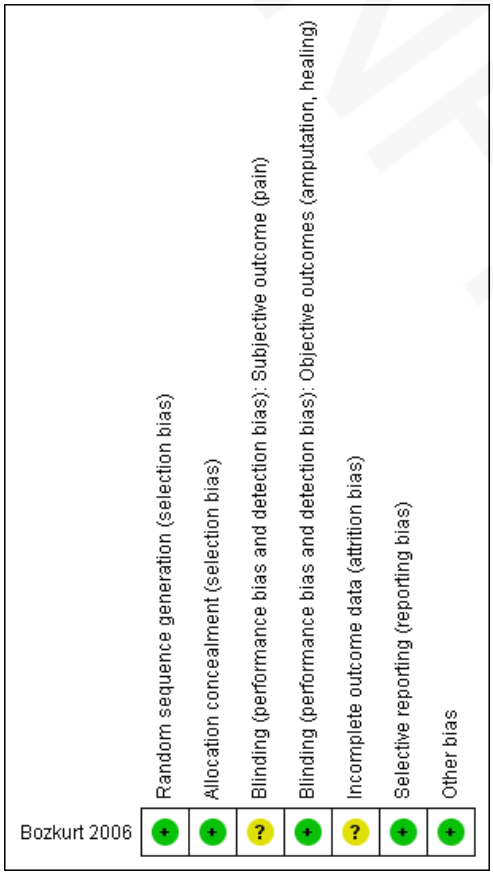
Figure 2



Caption

Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3



Caption

Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Sources of support

Internal sources

- Christian Medical College, Vellore, India
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- Prof. BV Moses & ICMR Centre for Advanced Research in Evidence-Informed Healthcare, India
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CONFIDENTIAL DRAFT

Feedback

Appendices

1 CENTRAL search strategy

Search run on Wed Mar 29 2017		
#1	MESH DESCRIPTOR Arteriosclerosis	869
#2	MESH DESCRIPTOR Arteriolosclerosis EXPLODE ALL TREES	0
#3	MESH DESCRIPTOR Arteriosclerosis Obliterans	72
#4	MESH DESCRIPTOR Atherosclerosis	645
#5	MESH DESCRIPTOR Arterial Occlusive Diseases	737
#6	MESH DESCRIPTOR Intermittent Claudication	726
#7	MESH DESCRIPTOR Ischemia	803
#8	MESH DESCRIPTOR Peripheral Vascular Diseases EXPLODE ALL TREES	2236
#9	(atherosclero* or arteriosclero* or PVD or PAOD or PAD):TI,AB,KY	9509
#10	((arter* or vascular or vein* or veno* or peripher*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	8385
#11	(peripheral near3 dis*):TI,AB,KY	3533
#12	(claudic* or IC):TI,AB,KY	3229
#13	(isch* or CLI):TI,AB,KY	24788
#14	arteriopathic or leriche*:TI,AB,KY	65
#15	dysvascular*:TI,AB,KY	11
#16	(leg near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	99
#17	(limb near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	158
#18	((lower near3 extrem*) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*)):TI,AB,KY	82
#19	MESH DESCRIPTOR Leg EXPLODE ALL TREES WITH QUALIFIERS BS	1113
#20	MESH DESCRIPTOR Iliac Artery	147
#21	MESH DESCRIPTOR Popliteal Artery	282
#22	MESH DESCRIPTOR Femoral Artery	834
#23	MESH DESCRIPTOR Tibial Arteries	33
#24	(((femor* or iliac or popliteal or fempop* or crural or poplite* or infrapopliteal or inguinal or femdist* or inguinal or infrainquinal or tibial) near3 (occlus* or reocclus* or re-occlus* or steno* or restenos* or obstruct* or lesio* or block* or harden* or stiffen* or obliter*))):TI,AB,KY	1220
#25	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 or #24	45798
#26	MESH DESCRIPTOR Sympathectomy EXPLODE ALL TREES	136
#27	sympathectom*:TI,AB,KY	231
#28	MESH DESCRIPTOR Lumbosacral Plexus EXPLODE ALL TREES	877
#29	(lumbosacral plexus):TI,AB,KY	140
#30	#26 OR #27 OR #28 OR #29	1125
#31	MESH DESCRIPTOR Prostaglandins EXPLODE ALL TREES	4794
#32	MESH DESCRIPTOR Thromboxanes EXPLODE ALL TREES	744
#33	*prosta*:TI,AB,KY	19951

#34	PGE*:TI,AB,KY	1846
#35	PGI*:TI,AB,KY	765
#36	(AS-013 or ventavis or TTC-909):TI,AB,KY	8
#37	thrombox* :TI,AB,KY	1528
#38	#31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37	22496
#39	#25 AND #30 AND #38	6

2 Trials registries searches

CT.gov

1 study found for: lumbar sympathectomy

WHO

No results were found for: lumbar sympathectomy

ISRCTN

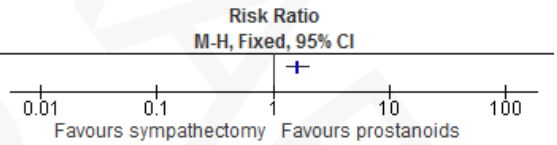
No results were found for: lumbar sympathectomy

Graphs

1 - Prostanoids versus lumbar sympathectomy

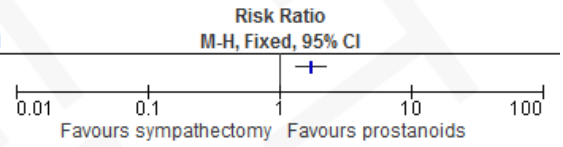
1.1 Complete ulcer healing without rest pain or major amputation at 24 weeks (per-protocol analysis)

Study or Subgroup	Prostanoids Events	Total	Sympathectomy Events	Total	Risk Ratio M-H, Fixed, 95% CI
Bozkurt 2006	72	84	41	78	1.63 [1.30, 2.05]



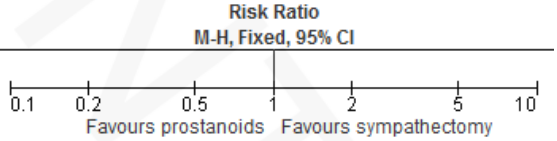
1.2 Complete ulcer healing without rest pain or major amputation at 24 weeks (ITT/sensitivity analysis)

Study or Subgroup	Prostanoids Events	Total	Sympathectomy Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bozkurt 2006	72	100	41	100		1.76 [1.35, 2.29]



1.3 Mortality (per-protocol analysis)

Study or Subgroup	Prostanoids Events	Total	Sympathectomy Events	Total	Risk Ratio M-H, Fixed, 95% CI
Bozkurt 2006	0	84	0	78	Not estimable



1.4 Mortality (ITT/sensitivity analysis)

Study or Subgroup	Prostanoids Events	Total	Sympathectomy Events	Total	Risk Ratio M-H, Fixed, 95% CI
Bozkurt 2006	16	100	22	100	0.73 [0.41, 1.30]